



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,913	08/04/2003	C. Frank Bennett	ISPH-0757	7573

7590 03/10/2005

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

EXAMINER

ASHEN, JON BENJAMIN

ART UNIT	PAPER NUMBER
----------	--------------

1635

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

JLC

Office Action Summary	Application No. 10/633,913	Applicant(s) BENNETT ET AL.	
	Examiner Jon B. Ashen	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 4-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/04/2003</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

1. Claims 1, 2 and 4-15 are pending in this application. Claims 3 and 16-20 were cancelled by Applicant in the communication filed 01/26/2004. Claims 1, 2 and 4-15 are currently under examination in this Application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 15 is rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of NAC in cells or tissues comprising contacting said cells or tissues with the antisense compound of claim 1 *in vitro*, does not reasonably provide enablement for this method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples

and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claim 15 is drawn broadly to a method of inhibiting the expression of NAC in cells or tissues comprising contacting said cells or tissues with the antisense compound of claim 1 and reads on *in vivo* embodiments. The nature of the instant invention is a method of nucleic acid therapy which results in inhibition of any NAC in any cells or tissues using an antisense compound that is an antisense oligonucleotide which specifically targets and inhibits the expression of human NAC (SEQ ID NO: 3).

The specification provides a set of examples wherein cells *in vitro* (cell culture) are treated with antisense oligonucleotides targeted to SEQ ID NO: 3 and the expression of SEQ ID NO: 3 is inhibited (pg. 85, Table 1). The specification, however, does not provide any examples that demonstrate *in vivo* administration of the claimed antisense compound so as to achieve a biological effect commensurate with what is now claimed, which is the *in vivo* inhibition of the expression of NAC in any cells or tissues of any organism by any mode of administration.

The state of the art at the time the instant invention was made, relative to the enablement of the antisense therapies *in vivo*, recognizes that there is a high degree of unpredictability in the art of applying antisense without direct evidence of therapeutic effect due to obstacles that continue, to the present day, to hinder the application of nucleic acid therapies *in vivo* (whole organism). Such obstacles include, for example, problems with delivery and target accessibility (see Opalinska et al., Check, Jen et al. below). Cell culture examples are generally not predictive of *in vivo* inhibition due to

Art Unit: 1635

differences in metabolites and clearance rates, local concentration of antisense, and the potential for non-antisense side effects. The field of antisense generally, to date, does not provide guidelines by which antisense can be routinely targeted to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a particular and desired biological effect. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic antisense method.

Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514) provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511).

In regards to the delivery of therapeutic nucleic acids, Jen et al. (Stem Cells 2000, Vol. 18, p 307-319) state (pg. 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (pg. 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Check also states, in regards to delivery, that ""Scientists tried a variety of ways to get the antisense RNAs into cells [B]ut antisense has not performed well in clinical trials, partly because these delivery systems were not particularly effective. Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. "But we've looked at a lot of the delivery methods that have been used for antisense and so far I haven't been impressed," she says" (pg 11, col. 3, lines 4-15).

The specification has provided limited guidance for one skilled in the art to practice the invention claimed. However, this guidance would not have been sufficient to enable the skilled artisan, at the time of filing, to have practiced the instant method over the broad scope claimed. One of the major hurdles to the *in vivo* (whole organism) application of antisense is the delivery of an antisense molecule to a target cell at a concentration effective to achieve a particular and desired biological effect. Although antisense is considered to be a potential therapeutic, there are art-recognized

limitations to its applicability *in vivo* (whole organism), particularly in regards to delivery, *in vivo* (whole organism) stability, *in vivo* accessibility and toxicity.

The examples in the specification which demonstrate specific antisense effects provide guidance by which such an effect is provided *in vitro*, when antisense can be delivered directly to cell cultures, but do not address the full scope of the instantly claimed methods. Given the unpredictability of antisense methods of treatment *in vivo* (whole organism), it is unclear that the *in vitro* examples using NAC antisense to inhibit the expression of NAC *in vitro* would correlate with the inhibition of NAC expression *in vivo* (whole organism) using the antisense compound targeted to SEQ ID NO: 3. To overcome the limitations to the *in vivo* (whole organism) application of antisense, one skilled in the art would require specific guidance to predictably apply antisense *in vivo*, to achieve a particular and desired biological effect. The specification does not provide this specific guidance for *in vivo* delivery of antisense to achieve a particular and desired biological effect nor did the antisense field, at the time the instant invention was made, have such general guidelines.

In order to practice the invention, over the full scope claimed, one skilled in the art would have needed to perform undue *de novo* trial and error experimentation, beyond the teachings of the instant specification, in order to determine how to specifically deliver antisense targeted to human NAC *in vivo*, to any cell or tissue type in any organism, at a concentration effective to provide the particular and desired biological effect as claimed. This undue *de novo* trial and error experimentation would include the determination of such factors as dosage, route of administration, disposition

Art Unit: 1635

of the antisense molecule in tissues, and the half-life and stability of the antisense molecule *in vivo* (whole organism) for the delivery of antisense targeted to NAC by an unspecified means to generally any target cell or tissue. Given the art recognized unpredictability of the application of antisense *in vivo* (whole organism) this determination would not be routine, nor would the limited guidance provided for NAC antisense delivered directly *in vitro* be sufficient for one skilled in the art to deliver antisense *in vivo*, to generally any target cell or tissue.

Therefore, based on the nature of the invention as a method of nucleic acid therapy, the breadth of the claimed method that encompasses *in vivo* inhibition of NAC in any organism, the lack of guidance and working examples of how the skilled artisan would carry out *in vivo* inhibition of NAC such that it would be successful any organism and the lack of predictability in the art of *in vivo* antisense therapy, an undue amount of *de novo* trial and error experimentation would be required to practice the instant method commensurate with the full scope of what is now claimed. Therefore, the inventors have not enabled one skilled in make and use the agent of the claimed invention.

Claim Rejections - 35 USC § 102 or 35 USC § 103

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Art Unit: 1635

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-2 and 4-14 are rejected under 35 U.S.C. 102(e) or 35 USC 103(a) as being anticipated by or obvious over Zhang et al. (U.S. Patent 6,258,600). The invention as set forth in claims 1-2 and 4-14 is drawn to a compound 8-50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human NAC (SEQ ID NO: 3) wherein said compound specifically hybridizes with and inhibits the expression of NAC (claim 1) wherein said compound can be an antisense oligonucleotide (claim 2) or a chimeric oligonucleotide (claim 10) wherein said compound comprises at least one modified internucleoside linkage (claim 4) that is a phosphorothioate linkage (claim 5), at least one modified sugar moiety (claim 6) that is a 2'-O-methoxyethyl moiety (claim 7) and at least one modified nucleobase (claim 8) that is a 5'-methylcytosine (claim 9) and a composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent (claim 12) wherein said composition further comprises a colloidal dispersion system (claim 13) and wherein said compound is an antisense oligonucleotide (claim 14) and to a compound 8-50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding NAC (claim 11).

Zhang et al. disclose SEQ ID NO: 85, a 20 bp antisense oligonucleotide that is a chimeric "gapmer" that is formulated in a pharmaceutically acceptable carrier and a colloidal dispersion system (liposomes) and that comprises phosphorothioate internucleoside linkages, 2'-O-methoxyethyl moieties and 5'-methylcytosines and is 90% complementary to the coding region of instant SEQ ID NO: 3 at positions 3175 to 3194 (col. 42, Example 15 and table 1 including legend). The antisense oligonucleotide of Zhang et al. targets and specifically hybridizes with at least an 8-nucleobase portion of an active site as disclosed by Applicant (instant specification: pg. 85, Table 1; pg. 87, 1st full paragraph) on a nucleic acid molecule encoding NAC.

Furthermore, since the prior art oligonucleotide meets all the structural limitations of the claims, the prior art oligonucleotide comprises an antisense oligonucleotide that is targeted to the coding region of SEQ ID NO: 3 and to an active site within that coding region as identified by Applicant, and will specifically hybridize with and inhibit the expression of NAC, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic.

Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Therefore, the instant invention is anticipated or obvious over Zhang et al. (U.S. Patent 6,258,600).

6. Claims 1-2 and 4-14 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Cowser (U.S. Patent 5,962,672). The invention as set forth in claims 1-2 and 4-14 is outlined in a previous rejection herein. Cowser discloses SEQ ID NO: 29, a 20 bp antisense oligonucleotide that is a chimeric "gapmer" that is formulated in a pharmaceutically acceptable carrier and a colloidal dispersion system (liposomes) and that comprises phosphorothioate internucleoside linkages, 2'-O-methoxyethyl moieties and 5'-methylcytosines and is 83.3% complementary to the coding region of instant SEQ ID NO: 3 at positions 1622-1642 (cols. 28-29, example 15, Table 2). The antisense oligonucleotide of Cowser targets and specifically hybridizes with at least an 8-nucleobase portion of an active site as disclosed by Applicant (instant specification: pg. 85, Table 1; pg. 87, 1st full paragraph) on a nucleic acid molecule encoding NAC.

Furthermore, since the prior art oligonucleotide meets all the structural limitations of the claims, the prior art oligonucleotide comprises an antisense oligonucleotide that is targeted to the coding region of SEQ ID NO: 3 and to an active site within that coding region as identified by Applicant, and will specifically hybridize with and inhibit the

Art Unit: 1635

expression of NAC, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Therefore, the instant invention is anticipated or obvious over Cowsert (U.S. Patent 5,962,672).

7. Claims 1-2, 4-6, 8 and 12-14 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Arnold, Jr. et al. (U.S. Patent 5,955,597). The invention as set forth in claims 1-2, 4-6 and 12-14 is outlined in a previous rejection herein. Arnold, Jr. et al. disclose SEQ ID NO: 7, a 16 bp chemically synthesized oligomer that is an antisense oligonucleotide that can be formulated in a pharmaceutically acceptable carrier and a colloidal dispersion system and that can comprise phosphorothioate internucleoside linkages, modified sugar moieties, modified nucleobases and is 94% complementary to the coding region of instant SEQ ID NO: 3

Art Unit: 1635

at positions 1180-1195 (col. 39; col. 3, lines 19-38, lines 60-67; col. 5, lines 60-63; col. 6 lines 66-67 bridge to col. 7, lines 1-25; col. 8, lines 3-14; col. 14, lines 42-50; col. 15, lines 49-67; col. 16, lines 15-30 and col. 29, lines 49-51).

Furthermore, since the prior art oligonucleotide meets all the structural limitations of the claims, the prior art oligonucleotide comprises an antisense oligonucleotide that is targeted to the coding region of SEQ ID NO: 3 and to an active site within that coding region as identified by Applicant, and will specifically hybridize with and inhibit the expression of NAC, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Therefore, the instant invention is anticipated or obvious over Arnold, Jr. et al. (U.S. Patent 5,955,597).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed (US 20020192643 A1, filed September 1st, 1999) in view of Bennett et al. (U.S. Patent 5,998,148) and Baracchini et al. (5,801,154). The invention as set forth in claims 1-2, 4-10 and 12-15 is outlined in a previous rejection herein.

Reed teaches antisense targeted to a full length or portions of an NAC coding strand (pg. 10, [0096] antisense that comprises a nucleoside analog (pg. 10, [0092])). Reed specifically teaches targeting SEQ ID NO: 1, 3 or 5, each of which include a

Art Unit: 1635

coding region and a stop codon region (defined as including anything within about 50 nucleotides 5' of the stop codon) of a nucleic acid encoding NAC which includes sequence identical to the coding and stop codon regions of SEQ ID NO: 3 of the instant application. Reed teaches the desirability and art recognized need of understanding the relationship of NAC protein with other apoptotic proteins for devising useful therapies related to apoptosis and other cellular processes wherein he states that "Thus, knowledge about the proteins having domains that interact with and regulate caspases is important for devising strategies for manipulating cell life and death in therapeutically useful ways. The identification of such proteins that contain caspase-interacting domains and the elucidation of the proteins with which they interact, therefore, can form the basis for strategies designed to modulate apoptosis, cytokine production, cytokine receptor signaling, and other cellular processes. Thus a need exists to identify proteins that interact with caspases and other apoptosis related proteins. Reed does not teach antisense of the specific length of 8-50 nucleobases targeted to NAC or antisense targeted to a nucleic acid encoding NAC that comprises modified internucleoside linkages or that is a chimeric antisense molecule. Reed does not disclose specific nucleotide analogs.

Bennett et al. teach antisense of 8-30 nucleobases in length and teach modifications to antisense including 2'-O-methoxyethyl sugar modifications, 5-methylcytosine nucleobase modifications, chimeric oligonucleotides and modified internucleoside linkages including phosphorothioate linkages, to increase antisense stability and enhance affinity (col. 5; line 55 bridge thru to col. 10, line 25). Bennett et

Art Unit: 1635

al. teach making antisense targeted to the coding region of a target nucleic acid (col. 3, line 30 bridge to col. 4, line 57) and pharmaceutical carriers (col. 12 beginning at line 41) and colloidal dispersion systems (for example liposomes, col. 13, lines 10-15) for use in delivery of antisense compounds and methods of treating cells *in vitro* with antisense of the invention (col. 35, lines 20-28). Bennett et al. teach the process for designing antisense oligonucleotides that target a particular nucleic acid and that this process includes determination of a site or sites within this gene for the oligonucleotide interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result (col. 3, line 31 thru col. 4, line 57). Bennett et al. teach that, "Antisense compounds are commonly used as research reagents and diagnostics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. Antisense compounds are also used, for example, to distinguish between functions of various members of a biological pathway. Antisense modulation has, therefore, been harnessed for research use" (col. 5, lines 25-35).

Baracchini et al. teach antisense of 8-30 nucleobases in length and teach modifications to antisense including 2'-O-methoxyethyl sugar modifications, 5-methylcytosine nucleobase modifications, chimeric oligonucleotides and modified internucleoside linkages including phosphorothioate linkages, to increase antisense stability and enhance affinity (see for example, cols. 6, line 35 bridge to col. 9, line 5.) Baracchini et al. teach making antisense targeted to the coding region of a target

Art Unit: 1635

nucleic acid (col. 9, lines 5-67) and pharmaceutical carriers (col. 4, lines 36) and colloidal dispersion systems (for example liposomes, col. 4, line 29) for use in delivery of antisense compounds and methods of inhibiting gene expression by delivering antisense to cells *in vitro* (cols. 5 and 6; col. 17, example 3). Baracchini et al. also teach the process for designing antisense oligonucleotides that target a particular nucleic acid and that this process includes determination of a site or sites within this gene for the oligonucleotide interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result (col. 9, line 5 thru col. 10, line 25).

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an antisense oligonucleotide targeted to a portion of the coding region of a nucleic acid encoding NAC of SEQ ID NO: 3 (as taught by Reed) of a length within the range of 8-50 nucleobases (as taught by Bennett et al. and Baracchini et al.) because antisense of short length are more easily synthesized and easier to deliver to cells and because antisense of this size was the convention in the art (as exemplified by Bennett et al. and Baracchini et al.) and because Bennett et al. and Baracchini et al. specifically teach targeting coding regions with antisense (see Bennett et al., col. 3, line 31 thru col. 5, line 24 and Baracchini et al., col. 9, line 6 thru col. 10, line 19) and because Reed specifically teaches making antisense targeted to SEQ ID NO: 1, 3 or 5 of their specification, which contains the coding region of a nucleic acid encoding NAC of SEQ ID NO: 3 of the instant application. Any antisense targeted to the coding region of SEQ ID NO: 1, 3 or 5 of Reed would have been targeted to the

Art Unit: 1635

coding region of instant SEQ ID NO: 3. Moreover, the teaching of the instant specification appears to parallel the teachings of Bennett et al. and Baracchini et al. (see pg. 6, line 1 thru pg. 9, line 29) which further shows that the teachings of Bennett et al. and Baracchini et al. were well known in the art at the time the instant invention was made. It would also have been obvious to construct antisense molecules with modifications that were well known and routine in the art that were 2'-methoxyethyl modifications, phosphorothioate modifications and 5'-methylcytosine modifications and modifications to produce chimeric oligonucleotides because such modifications were known to enhance stability, uptake and affinity of antisense molecules (see Bennett et al. col. 5, lines 45-55 and Baracchini et al., col. 6, lines 20-34, for example) and because Reed teaches antisense targeted to NAC that can comprise nucleoside analogs. It would have been obvious to one of ordinary skill in the art to make a composition comprising antisense targeted to NAC and a pharmaceutically acceptable carrier including a colloidal dispersion system because pharmaceutically acceptable carriers and colloidal dispersion systems were well known and used routinely in the art of delivering antisense molecules to cells *in vitro* and because Reed teaches providing NAC antisense in compositions which aid delivery of antisense across a cell membrane (pg. 10, [0093]). It would also have been obvious to one of ordinary skill in the art to use antisense targeted to the coding region of a nucleic acid encoding NAC of SEQ ID NO: 3 in a method of inhibiting NAC expression in cells *in vitro* because Reed teaches using antisense targeted to NAC to inhibit the expression of cells *in vitro* and it would be

an obvious use of an antisense oligonucleotide designed to hybridize with and inhibit the expression of a nucleic acid encoding NAC of SEQ ID NO: 3.

One of ordinary skill in the art would have been motivated to make an antisense molecule targeted to a coding region of a nucleic acid encoding NAC of SEQ ID NO: 3 and to use that molecule in a method of inhibiting gene expression because Reed explicitly teaches inhibiting the expression of NAC in cells *in vitro* using antisense targeted to sequences consisting of the coding region of a nucleic acid encoding NAC of SEQ ID NO: 3 and because Reed teaches the importance of increasing knowledge about proteins that interact with and regulate caspases for devising strategies for useful therapies and because Bennett et al. teach the use, by those of ordinary skill in the art, of antisense to elucidate the function of particular genes to distinguish between functions of various members of a biological pathway. One of ordinary skill in the art would have, therefore, been motivated to use antisense to NAC to elucidate the functions of NAC, as a protein that interacts with caspases, in order to devise a strategy for a useful therapy and to distinguish those functions between NAC and other various members of that biological pathway.

One of ordinary skill in the art would have expected success in constructing antisense targeted to the coding region of a nucleic acid encoding NAC of SEQ ID NO: 3, which inhibits the expression of NAC, because the sequence of the NAC coding region was known in the art and because the process of designing antisense oligonucleotides that target a particular nucleic acid, including a determination of a site or sites within this gene for the oligonucleotide interaction to occur such that the desired

effect will result, was well known in the art (as taught by both Bennett et al. and Baracchini et al.). One of ordinary skill in the art would have expected success in using the abovementioned antisense oligonucleotide in a method of inhibiting gene expression *in vitro* because such methods were also well known and routine in the art (as exemplified by Bennett et al. and Baracchini et al.).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

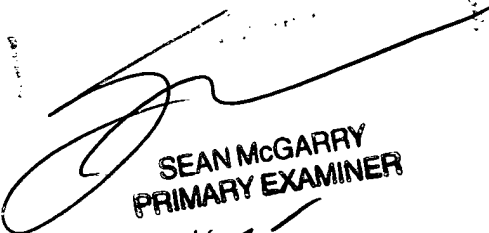
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

Art Unit: 1635

problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba



SEAN MCGARRY
PRIMARY EXAMINER
1635